INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000529

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/25 C07K14/60 G01N33/74 A61P1/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/92292 A (BEDNAREK MARIA ; MERCK & CO INC (US)) 6 December 2001 (2001-12-06) page 5, line 30 - page 6, line 6 page 15, lines 13-34	1-73, 77-82
X	EP 1 186 293 A (PFIZER PROD INC) 13 March 2002 (2002-03-13) paragraphs '0054!, '0063!	1,15-20, 26,27,32
X	WO 01/56592 A (NOVO NORDISK AS) 9 August 2001 (2001-08-09) page 7, lines 16-22; claims 7,13	38-73, 77-82
Y	page 3, lines 22-30; claim 16	1-37

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2004	13/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Durrenberger, A

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WREN A M ET AL: "GHRELIN ENHANCES APPETITE AND INCREASES FOOD INTAKE IN HUMANS" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, NEW YORK, NY, US, vol. 86, no. 12, December 2001 (2001-12), pages 5992-5995, XP001156529 ISSN: 0021-972X cited in the application page 5992, right-hand column page 5994, right-hand column, paragraph 2 - page 5995	48-73, 77-82
X	NAGAYA NORITOSHI ET AL: "Ghrelin improves left ventricular dysfunction and cardiac cachexia in heart failure." CURRENT OPINION IN PHARMACOLOGY, vol. 3, no. 2, April 2003 (2003-04), pages 146-151, XP002311021 ISSN: 1471-4892 page 146, right-hand column, paragraphs 2,3 page 147, right-hand column, paragraph 2	38-73, 77-82
Y	page 149, left-hand column, paragraph 2	1-37
X	US 5 798 337 A (MCDOWELL ROBERT S ET AL) 25 August 1998 (1998-08-25) column 30, lines 44,45 column 31, lines 62-67	1,15-20, 26,27,32
X	VAN DEN BERGHE GREET: "Growth hormone secretagogues in critical illness" HORMONE RESEARCH (BASEL), vol. 51, no. Suppl. 3, November 1999 (1999-11), pages 21-28, XP009041731 & THE TENTH HGH SYMPOSIUM; SEVILLE, SPAIN; APRIL 23-24, 1999 ISSN: 0301-0163 page 24, right-hand column	74

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national application No.
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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 33-37, 75, 76 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000529

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0192292	A	06-12-2001	CA	2411667 A1	06-12-2001
			EP	1353683 A2	22-10-2003
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			DE	69518000 D1	17-08-2000
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			EP	0999220 A2	10-05-2000
			ES	2150018 T3	16-11-2000
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			IL	115994 A	28-09-2000
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			US	6034216 A	07-03-2000
			WO	9615148 A2	23-05-1996
			US	2003139348 A1	24-07-2003
			ZA	9509757 A	16-05-1997

AMENDED CLAIMS

[received by the International Bureau on 14 March 2005 (14.03.05);
claims 1 and 82 replaced by new claims 1-44 (7 Pages)]

1. Use of a ghrelin-like compound or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the prophylaxis or treatment of cancer cachexia in an individual in need of such treatment,
wherein the ghrelin-like compound comprises a structure defined by formula I

$Z^1 - (X^1)_m - (X^2) - (X^3)_n - Z^2$, wherein

Z^1 is an optionally present protecting group

each X^1 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

X^2 is any amino acid selected from naturally occurring and synthetic amino acids, said amino acid being modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

each X^3 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

wherein one or more of X^1 and X^3 optionally may be modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

Z^2 is an optionally present protecting group,

m is an integer in the range of from 1-10

n is 0 or an integer in the range of from 1-35,

and wherein:

(a) said ghrelin-like compound or pharmaceuticaly acceptable salt thereof is 27-28 amino acids in length, with the proviso that said ghrelin-like compound is at least 80 % homologous to SEQ ID NO 1, such as at least 85 % homologous to SEQ ID NO: 1

and/or

(b) said ghrelin-like compound is at least 90 % homologous to SEQ ID NO 1.

2. The use according to claim 1, wherein said ghrelin-like compound is at least 95 % homologous to SEQ ID NO 1.

3. The use according to claim 1, wherein said ghrelin-like compound is at least 98 % homologous to SEQ ID NO 1.

4. The use according to any of the preceding claims, wherein m is an integer in the range of from 1-9, such as of from 1-8, such as of from 1-7, such as of from 1-6, such as of from 1-5, such as of from 1-4, such as of from 1-3, such as of from 1-2, such as 2.

5. The use according to any of the preceding claims, wherein X^2 is selected from the group of modified Ser, modified Cys and modified Lys, such as wherein X^2 is modified Ser.

6. The use according to any of the preceding claims, wherein the ghrelin-like compound is selected from a compound of

formula II Z^1 – Gly- $(X^1)_{m-1}$ – (X^2) – $(X^3)_n$- Z^2,

formula III Z^1 – Gly- Ser – (X^2) – $(X^3)_n$- Z^2, and

formula IV Z^1 – Gly – (X^2) – $(X^3)_n$- Z^2.

7. The use according to claim 6, wherein the ghrelin-like compound is having formula III.

8. The use according to any of the preceding claims, wherein n is an integer in the range of from 1-25, such as of from 1-24, such as from 1-15, such as of from 1-10, such as of from 10-25, such as of from 10-24, such as of from 15-25, such as of from 15-24.

9. The use according to any of the preceding claims, wherein the acyl group is selected from a C1-C35 acyl group, such as a C1 – C20 acyl group, such as a C1 – C15 acyl group, such as a C6 – C15 acyl group, such as a C6 – C12 acyl group, such as a C8 – C12 acyl group.

10. The use according to any of the preceding claims, wherein the acyl group is selected from the group of C7 acyl group, C8 acyl group, C9 acyl group, C10 acyl group, C11 acyl group, and C12 acyl group.

11. The use according to any of the preceding claims, wherein the acyl group is selected from the group of C8 acyl group, and C10 acyl group.

12. The use according to any of the preceding claims, wherein the acyl group is selected from the group of C7 acyl group, C9 acyl group, and C11 acyl group, such as from the group of C9 acyl group and C11 acyl group.

13. The use according to claim 1, wherein the ghrelin-like compound is ghrelin or a pharmaceutically acceptable salt thereof.

14. The use according to to claim 1, wherein the ghrelin-like compound has SEQ ID NO: 1, SEQ ID NO: 2, or SEQ ID NO: 3.

15. The use according to any of the preceding claims, wherein the medicament is in a formulation for subcutaneous administration.

16. The use according to any of the preceding claims, wherein the formulation comprises the ghrelin-like compound or a salt thereof as a lyophilisate and the formulation further comprises a solvent, said lyophilisate and said solvent being in separate compartments until administration.

17. The use according to any of the preceding claims, wherein the formulation is a solution of the ghrelin-like compound or a salt thereof.

18. The use according to claim 16 or 17, wherein the solvent is saline.

19. The use according to any of the preceding claims, wherein the medicament is administered prior to or during a meal.

20. The use according to any of the preceding claims, wherein the medicament is administered in a concentration equivalent to from 10 ng to 10 mg ghrelin per kg bodyweight.

21. The use according to claim 20, wherein the medicament is administered in a concentration equivalent to from 0.1 μg to 1 mg ghrelin per kg bodyweight, such as from 0.5 μg to 0.5 mg ghrelin per kg bodyweight, such as from 1.0 μg to 0.1 mg ghrelin per kg bodyweight, such as from 1.0 μg to 50 μg ghrelin per kg bodyweight, such as from 1.0 μg to 10 μg ghrelin per kg bodyweight.

22. The use according to claim 21, wherein the medicament is administered in a concentration equivalent to from 0.1 μg to 1 mg ghrelin per kg bodyweight, such as from 0.5 μg to 0.5 mg ghrelin per kg bodyweight, such as from 1.0 μg to 0.1 mg ghrelin per kg bodyweight, such as from 1.0 μg to 50 μg ghrelin per kg bodyweight, such as from 1.0 μg to 10 μg ghrelin per kg bodyweight.

23. The use according to any of the preceding claims, wherein the medicament is administered as a bolus prior to or during a meal, said bolus comprising an amount of the ghrelin-like compound or a salt thereof equivalent to from 0.3 μg to 600 mg ghrelin

24. The use according to claim 23, wherein the medicament is administered as a bolus prior to or during a meal, said bolus comprising an amount of the ghrelin-like compound or a salt thereof equivalent to from 2.0 μg to 200 mg ghrelin, such as from 5.0 μg to 100 mg ghrelin, such as from 10 μg to 50 mg ghrelin, such as from 10 μg to 5 mg ghrelin, such as from 10 μg to 1.0 mg ghrelin.

25. The use according to any of the preceding claims, wherein the medicament is administered from one to three times daily, each administration being during a meal or at the most 180 minutes prior to a meal, such as at the most 90 minutes prior to a

meal, e.g. at the most 45 minutes prior to a meal, such as at the most 30 minutes prior to a meal, such as at the most 25 minutes prior to a meal, such as at the most 20 minutes prior to a meal, such as at the most 15 minutes prior to a meal, such as at the most 10 minutes prior to a meal, such as at the most 5 minutes prior to a meal.

26. The use according to claim 25, wherein the medicament is administered three times daily.

27. The use according to any of the preceding claims, wherein the cancer cachexia is caused by a catabolic disorder.

28. The use according to any of claims 1 to 26, wherein the cancer cachexia is caused by an anorectic disorder.

29. The use according to any of claims 1 to 27, where the individual is suffering from a cancer selected from lung cancer, pancreatic cancer, liver cancer, and GI tract cancers.

30. Use according to any of the preceding claims, wherein said medicament is administered in combination with a chemotherapy medicament.

31. The use according to any of the preceding claims, wherein the treatment or prevention of cancer cachexia leads to stimulation of appetite, stimulation of food intake, stimulation of weight gain or weight maintenance, and/or increased body fat mass.

32. A method for preventing or treating cancer cachexia, comprising administering to an individual in need thereof an effective amount of a ghrelin-like compound as defined in any of claims 1-14.

33. A method for preventing or treating cancer, comprising administering to an individual in need thereof an effective amount of a secretagogue as defined in any of claims 1-14, in combination with an anti-neoplastic treatment.

34. The method according to claim 33, wherein the antineoplastic treatment is radiotherapy.

35. The method according to claim 33, wherein the antineoplastic treatment is chemotherapy.

36. The method according to any of claims 33-35, wherein the treatment or prevention of cancer cachexia leads to stimulation of appetite, stimulation of food intake, stimulation of weight gain or weight maintenance, and/or increased body fat mass.

37. A method for preventing or treating cachexia, comprising administering to an individual in need thereof an effective amount of a ghrelin-like compound and an effective amount of a NSAID medicament.

38. The method according to claim 37, wherein the ghrelin-like compound is as defined in any of claims 1 to 14.

39. Use of a ghrelin-like compound or a pharmaceutically acceptable salt thereof for the preparation of a medicament, in a formulation for subcutaneous administration, for stimulation of appetite in an individual by administering a subcutaneous dosage of said medicament to the individual,

wherein the ghrelin-like compound comprises a structure defined by formula I

$Z^1 - (X^1)_m - (X^2) - (X^3)_n - Z^2$, wherein

Z^1 is an optionally present protecting group

each X^1 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

X^2 is any amino acid selected from naturally occurring and synthetic amino acids, said amino acid being modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

each X^3 is independently selected from an amino acid, wherein said amino acid is selected from naturally occurring and synthetic amino acids,

wherein one or more of X^1 and X^3 optionally may be modified with a bulky hydrophobic group, preferably an acyl group, or a fatty acid,

Z^2 is an optionally present protecting group,

m is an integer in the range of from 1-10

n is 0 or an integer in the range of from 1-35.

40. Use according to claim 39, wherein the ghrelin-like compound is as defined in any of claims 1-14.

41. Use according to claim 40, wherein the formulation is as defined in any of claims 15-19.

42. Use according to claim 41, wherein the solvent is saline.

43. Use according to any of claims 39 to 42, wherein the medicament is administered as defined in any of claims 19-26.

44. Use according to any of claims 39-43, wherein said individual is suffering from lipodystrophy.